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THE INFLUENCE OF POSTURE ON PARACETAMOL ABSORPTION

The rate of gastric emptying probably determines the rate of absorption of most orally administered drugs and it follows that factors influencing gastric emptying rate will in turn influence the rate of drug absorption (Prescott, 1974; Nimmo, 1976; Nimmo, Heading, Wilson, Tothill & Prescott, 1975). In neonates, the stomach empties more rapidly in the prone and right lateral positions than in the supine and left lateral positions (Yu, 1975), but there is little data in man relating gastric emptying or drug absorption with posture. The rate of paracetamol absorption correlates well with gastric emptying rate, and in the present report we describe the effect of posture on the rate of paracetamol absorption.

Eight healthy volunteers with a mean ± s.d. age of 29 ± 1.8 years and a mean ± s.d. weight of 68.8 ± 8.2 kg were studied twice. On one occasion the subjects were ambulant throughout the study and on the other they lay on the left side for 2 h and were then ambulant. On both occasions, after an overnight fast, each subject was given 1.5 g paracetamol as three Panadol tablets with 200 ml water. Blood samples were taken at intervals for 4 h for paracetamol measurements (Prescott, 1971). No food, fluid or tobacco was allowed during the study. Statistical analyses were carried out using the paired Student's *t*-test.

Paracetamol absorption was significantly delayed in all subjects lying on the left side (Figure 1). Plasma concentrations (mean ± s.e. mean) at 15 min and 30 min in the supine subjects were only 0.18 ± 0.18 μg/ml and 7.8 ± 3.1 μg/ml respectively and 12.5 ± 4.8 μg/ml and 20.8 ± 3.3 μg/ml in the ambulant subjects ($P < 0.05$ and < 0.01 respectively). Plasma concentrations after 45 min did not differ in the two groups.

The total amount of paracetamol absorbed in 4 h was not influenced by posture since the mean area under the plasma concentration time curve (0–4 h) was 49.5 ± 4.3 μg ml^{-1} h in the ambulant study and 45.5 ± 2.8 μg ml^{-1} h in the supine study.

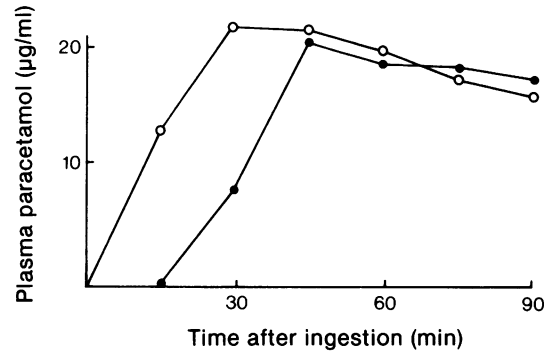

Figure 1 Mean plasma paracetamol concentrations after 1.5 g orally in ambulant (○) and supine (●) subjects ($n = 8$).

The delay in paracetamol absorption observed in subjects lying on the left side was probably due to slower gastric emptying in that position. Martin (1971) commented on a similar delay in the absorption of aspirin solution in five subjects in the 'left supine position' and also attributed this to delayed gastric emptying. Unfortunately no plasma concentration data was given. Patients who take tablets while in bed on their left side will be likely to have delayed absorption and it is obvious that the position of subjects must be taken into account in drug absorption studies.

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PHYSICAL EXERCISE AND DISPOSITION OF DIAZEPAM

Diazepam, a widely used tranquilizer, exhibits strong binding to plasma and tissues. Its hepatic elimination is relatively slow (low hepatic extraction ratio) and independent of the liver blood flow (Klotz, Antonin & Bieck, 1976). With antipyrine, the non protein-bound model drug for hepatic elimination, significant differences in the volumes of distribution have been reported, if the subjects were exposed to heat and/or physical stress (Swartz, Sidell & Cucinell, 1974). In subjects performing physical exercise for 2 h an increase in V_d with a reciprocal fall in k_{el} resulting in an unchanged clearance rate was found with amylobarbitone (Balasubramanian, Mawer & Simons, 1970). We used diazepam as a kind of prototype for a drug with blood-flow independent elimination and extensive binding, to compare in healthy subjects the pharmacokinetics of this drug during rest and after maximal short-term stress. The blood perfusion of the different organs and tissues can change under these two experimental conditions. Consequently, the plasma level-time profile and the disposition of the drug might be altered by distribution changes or re-mobilization from a storage site.

Four healthy volunteers (25–30 years, 53–72 kg) received a single intravenous bolus of 0.1 mg diazepam/kg. Maximal exercise was performed in the sitting position on a computerized bicycle (dynavit®, meditronic) which calculated according to the age, weight and sex of the individuals the corresponding maximal heart rates. The work-load was progressively and automatically adjusted to maintain the continuously monitored heart rate for 5 min in this maximal range. Immediately before and after this physical stress venous blood samples were drawn into heparinized tubes from an indwelling catheter, or by venepuncture at 0.5, 1, 2, 4, 7, 10, 24, 36, 48, 60 and 72 h after administration. Subjects remained in the supine position for the first 10 h, except at the time of the test. Concentrations of diazepam were assayed in the different plasma samples by a specific and sensitive gaschromatographic procedure (Klotz, Avant, Hoyumpa, Schenker & Wilkinson, 1975). The plasma level-time curves were fitted according to a two compartment open model by the least squares iterative digital computer program SAAM-25 (Berman & Weis, 1974). This model and its pharmacokinetic parameter have been well described (Riegelman, Loo & Rowland, 1968). The biexponential decline of the plasma levels of diazepam after the single intravenous dose of 0.1 mg/kg in two representative individuals can be seen in Figure 1. The computer fitted curves, derived from the plasma concentrations measured just before and after the physical exercise, did not demonstrate statistically significant differences. The most important pharmacokinetic parameters calculated were also almost identical under the two experimental conditions (Table 1).

The motion of a patient taking diazepam can range from bed rest and moderate work to physical exercise. These different situations might alter the clinical response of the drug simply by changes in its distribution or elimination. After physical stress, changes in cardiac output can be observed. This can influence a drug's disposition via changes in an organ's or tissue's blood perfusion (Wilkinson, 1975). Hepatic elimination can be modified by changes in hepatic blood flow (Rowland, Benet & Graham, 1973) and during exercise this flow decreases. Since diazepam belongs to the group of drugs whose elimination is independent of the liver blood flow (Klotz *et al.*, 1975), it is not surprising that its total body clearance (Cl) and its half-life of elimination ($T_{\frac{1}{2}}\beta$) were unaffected by physical exercise. In addition, at the different times of blood sampling no significant increases or decreases in the plasma levels

Table 1 Pharmacokinetic parameters (mean ± s.d.) of diazepam as calculated from blood samples drawn before and after physical stress

Parameter	*Before exercise*	*After exercise*
$T_{\frac{1}{2}}\alpha$(h)	1.3 ± 0.3	1.1 ± 0.7
$T_{\frac{1}{2}}\beta$(h)	35.3 ± 3.0	29.8 ± 9.2
Cl(ml/min)	21.7 ± 2.9	26.3 ± 4.8
V_d (l/kg)	0.96 ± 0.10	0.98 ± 0.24
$V_d\beta$ (l/kg)	1.02 ± 0.13	1.10 ± 0.28
V_1 (l/kg)	0.36 ± 0.06	0.45 ± 0.06